

## THE RELATIONSHIP BETWEEN CANNABIS USE AND PSYCHOTIC DISORDERS: A COMPREHENSIVE REVIEW OF CURRENT EVIDENCE

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**Abstract: Purpose:** To analyze the evidence on the relationship between cannabis use and the development of psychotic disorders. Also discuss clinical and preventive implications, and highlight areas for future research to improve the management of psychosis. **Methodology:** Bibliographic review was conducted between May and June 2023, in the Scielo and PubMed databases. The descriptors used were: cannabis, psychotic disorders and psychosis. From this search, 18 articles were selected for review. **Results:** It is evident that genetic and environmental factors, combined with the use of cannabis, can anticipate or contribute to the development of psychotic disorders. There is a dose-response relationship between substance use and psychosis, with a quantitative and qualitative increase in psychotic symptoms in cannabis users. Furthermore, there are indications of an association between substance use and the development of bipolar affective disorder, anxiety disorders and depression. **Final Considerations:** There is an intimate relationship between the use of cannabis and the occurrence of psychosis, being influenced by the age of onset of use, genetic and environmental factors.

**Keywords:** cannabis; Psychotic Disorders; Psychosis.

## INTRODUCTION

In the contemporary scenario, Cannabis is the most prevalent drug in the world, accounting for approximately 180.6 million users. Over the last two decades, there has been a significant increase in this statistic, with adolescents being the most susceptible to the use and chemical dependence of this drug (RONCERO C. et al, 2017). The association between the use of Cannabis and the occurrence of psychosis is a scientifically recognized fact, however, this topic raises numerous debates (CARVALHO C., VIEIRA-

COELHO M., 2022). It is observed that only a small percentage of Cannabis users develop psychotic episodes. This relationship, although existing, does not imply that the use of Cannabis is a necessary or sufficient condition to trigger such disorders (KREBS MO et al., 2019).

A common point of discussion is the argument that if Cannabis causes psychosis, the increase in drug use must correspond to a proportional increase in cases of psychotic disorders (GANESH S.; D'SOUZA D., 2022). However, several studies suggest that cannabis use may be a "risk factor" for the development of psychotic disorders, especially in people genetically predisposed to these types of disorders (MARCONI A. et al., 2016). Heavy use of cannabis, especially strains with high levels of tetrahydrocannabinol (THC), appears to be more strongly associated with the risk of psychosis, and the dose and frequency of cannabis use continue to be reliable indicators of the risk of developing the aforementioned disorders. (HAMILTON I.; MONAGHAN M., 2019; CARVALHO C., VIEIRA-COELHO M., 2022).

Faced with such a situation, it is important to identify risk factors and clinical characteristics that can predict patients with greater vulnerability (KREBS MO et al., 2019). However, overall, the evidence from epidemiological studies is strong enough to support a public health message that cannabis use may increase the risk of psychotic disorders (GAGE S. et al, 2016; MARCONI A. et al.,2016). It is important to emphasize that the early initiation of cannabis use can result in significant damage to neurocognitive functions, due to greater exposure of the Central Nervous System to drug consumption, thus increasing the risk of manifestation of psychosis and other psychiatric symptoms (RONCERO C. et al., 2017; HINDLEY G. et al., 2020).

Given the relevance of this topic, the objective of this review is to analyze the evidence on the relationship between cannabis use and the development and worsening of psychotic disorders, examining recent clinical, epidemiological and experimental studies that investigate the association between cannabis use and the incidence, prevalence, and progression of psychotic disorders, as well as the biological mechanisms underlying this relationship. Furthermore, it is intended to identify individual risk factors and vulnerabilities, discuss the clinical and preventive implications of this association, and highlight areas of future research and development in the field of psychiatry to improve understanding and management of psychotic disorders.

## METHODOLOGY

This is a bibliographic review conducted between May and June 2023. It was developed according to the criteria of the PVO strategy, an acronym that represents: population or research problem, variables and outcome. Used to prepare the research through the following guiding question: "What is the relationship between cannabis use and the development and worsening of psychotic disorders, and what are the underlying mechanisms, risk factors and clinical implications of this association, based on the evidence?". In this sense, according to the parameters mentioned above, the population or problem of this research refers to patients who use cannabis and, due to this, they may be susceptible to the prognosis of psychotic disorders, as well as they can also develop a complication and aggravate a previously diagnosed psychosis. Searches for articles were carried out through searches in the PubMed Central (PMC) and SciELO (Scientific Electronic Library Online) databases. The descriptors used were: cannabis; psychotic disorders and

psychosis. Such descriptors were associated with the Boolean operators: “AND” and “OR” forming the search strategy: cannabis AND (“psychotic disorders” OR psychosis). From this search, 884 articles were found; 861 in the PubMed database and 23 in the SciELO database; subsequently submitted to the selection criteria. Inclusion criteria were: articles in English, Portuguese and Spanish; published in the period from 2016 to 2022 and that addressed the themes proposed for this research, giving preference to systematic review studies, meta-analyses, randomized clinical trials and also observational studies. Exclusion criteria were: duplicate articles, available in abstract form, that did not directly address the studied proposal and that did not meet another inclusion criterion. After applying the inclusion and exclusion criteria, there were 16 articles from the PubMed database and 2 articles from the SciELO database, totaling 18 articles to compose the collection of this study.

## RESULTS

### PSYCHOTIC DISORDERS

Psychotic disorders, also known as psychosis, are defined by hallucinations and delusions, and may be associated with disorganization or thought disorders, and patient agitation (AUCOIN, M. et al., 2020; HASAN A. et al., 2019). Symptoms may be present in several psychotic disorders, including schizophrenia, bipolar affective disorder and major depression with psychotic features (HANIN C. et al., 2021; HASAN A. et al., 2019).

True hallucinations are defined as sensory or auditory perception without an external stimulus, but are experiences that are said to be real by the patient. Delusion can be conceptualized as a firm belief that diverges from convictions, it is based on false or

incomplete information, confabulation or dogma. (HANIN C. et al., 2021)

Psychosis has a direct impact on the patient’s well-being, interfering with quality of life and daily functioning. Furthermore, patients with psychotic disorders are at a significantly increased risk of medical comorbidities, which have a significant impact on mortality and morbidity (AUCOIN, M et al., 2020).

### CANNABINOID ACTION MECHANISM

Cannabis’ mechanism of action is driven by two main signaling pathways: THC AND CBD. When cannabis is inhaled or used orally, these pathways are linked at the brain level, mainly in the G protein, and connect with the cannabinoid receptors CB1 and CB2 (CHAYASIRISOBHON S., 2020). These, in turn, leverage proteins and assemble beta-arrestins, producing Camp and stimulating the Gq/11 pathways. This is done in the endocannabinoid system (ECS), where modulation takes place at orthosteric sites, the interaction is mainly with GPCRs and CRIP1a/b proteins, and endogenous cannabinoid lipids (eCBs) are responsible for activating THC and CBD receptors. (LU HC, MACKIE K., 2021)

Furthermore, THC is a psychotropic chemical compound, with the potential to modify the behavior of its users, influencing their way of thinking, perception and action.(CHAYASIRISOBHON S., 2020). CBD, on the other hand, is less linked to psychotic experiences and adverse effects, as it is a non-psychotropic chemical agent. (CHAYASIRISOBHON S., 2020; COHEN K. et al., 2019). Therefore, the use of cannabis causes changes in the central nervous system, however, there are few differences, compared to non-users, in cognitive performance (COHEN K. et al., 2019).

## CANNABIS AND PSYCHOTIC DISORDERS

There are over 70 cannabinoids found in the cannabis plant. According to the European Monitoring Center for Drugs and Drug Addiction (EMCDDA) in 2021, cannabis sativa is one of the most consumed recreational drugs in Europe, mainly by adolescents and young adults. Around 15.4% of the European population aged between 15 and 34 reported having used cannabis at least once in the last year. This scenario led to a significant increase in international studies on the benefits, harms and possible consequences of cannabis use (PEARSON NT; BERRY JH, 2019).

In addition to recreational use, “medical cannabis” has gained prominence as a possible treatment for various disorders and symptoms, such as generalized anxiety disorder, depression, chronic pain and nausea, although there is still scant evidence and insufficient data to prove its effectiveness. On the other hand, there is consistent evidence that associates cannabis use with the development of psychotic disorders, such as schizophrenia, and transient psychotic symptoms, such as suspiciousness, paranoia and hallucinations (PEARSON NT; BERRY JH, 2019; ZUNINI PAAS et al., 2022; ORTIZ-MEDINA MB et al., 2018; SIDELI L. et al., 2019). The severity and chronicity of such cannabis-related psychosis are directly linked to its use (PEARSON NT; BERRY JH, 2019; SIDELI L. et al., 2019).

Such conditions are twice as likely to occur while using the drug. The biological mechanisms underlying this association are still not fully understood, but it is known that they are related to the action of cannabis components on various receptors of the Endocannabinoid System, which plays an important role in preserving the homeostasis of the central nervous system, in cognition and memory, motor control and analgesia (PEARSON NT; BERRY JH, 2019; SIDELI

L. et al., 2019). It is important to emphasize that the presence of psychosis associated with the use of cannabis does not necessarily depend on the previous existence of other psychopathological conditions (ZUNINI PAAS et al., 2022; PEARSON NT; BERRY JH, 2019).

The use of cannabinoids activates the endocannabinoid system, a part of the brain responsible for processing these substances through its receptors and enzymes. THC, one of the components of cannabis, is responsible for effects such as euphoria, increased sociability and heightened senses. These effects can be experienced minutes after using the drug and can last for hours, remaining in the body for a few weeks. When continuous use is stopped, withdrawal signs such as insomnia, appetite disorders, anxiety and depression are common (SIDELI L. et al., 2019). Taking into account that schizophrenia is a psychotic disorder related to the neurodevelopment process and that there is interference of the endocannabinoid system in this process, the hypotheses about the use of cannabis, especially at younger ages, and the emergence of diseases resulting from this change in modulation are increasingly robust (GAGE S. et al., 2016; RYAN JE et al., 2020). Studies indicate that cannabis can increase the risk of schizophrenia by about 30%, and demonstrate a strong association between cannabis use and psychotic disorders, with a three times greater risk of schizophrenia and two times greater risk of other psychotic disorders in individuals who consume cannabis more frequently (GANESH S.; D’SOUZA D., 2022).

In addition, several genetic and environmental factors, combined with cannabis use, may contribute to the development of psychotic disorders (ZUNINI PAAS et al., 2022; ORTIZ-MEDINA MB et al., 2018). The interaction of cannabis with the dopaminergic system can trigger psychotic

symptoms (ORTIZ-MEDINA MB et al., 2018; PEARSON NT; BERRY JH, 2019). Studies have shown that the interaction of cannabis with polymorphic variants of the catechol-O-methyltransferase (COMT) gene and the Val158Met polymorphism are associated with the development of schizophrenia (ORTIZ-MEDINA MB et al., 2018; PEARSON NT; BERRY JH, 2019). Individuals who initiate cannabis use during adolescence and young adulthood appear to be more predisposed to later developing psychotic symptoms (ZUNINI PAAS et al., 2022; ORTIZ-MEDINA MB et al., 2018).

Studies conducted in Norway and Spain have shown that cannabis use is associated with a 3-year anticipation of psychotic symptoms. Another study, carried out in the United States, found that the probability of developing psychosis increased 2.2 times for users who used cannabis in the 5 years prior to the psychotic crisis. In India, analyzes indicate that cannabis users hospitalized due to psychotic crises had symptoms lasting twice as long compared to non-users. In addition, in Spain, it has been shown that users who stopped using cannabis after the first psychotic crisis showed a reduction in negative symptoms compared to those who did not stop using it (ZUNINI PAAS et al., 2022).

Systematic studies have demonstrated a relationship between cannabis use and the onset of psychotic disorders, including long-term ones, as well as a dose-response relationship in terms of duration and/or frequency of use. A meta-analysis published in 2016 revealed an approximately 4-fold increase for more frequent and heavy users, and a 2-fold increase for moderate users compared to non-users. In addition to the quantitative increase in events, studies also showed a qualitative increase, that is, an exacerbation of psychotic symptoms in these

users (HAMILTON I.; MONAGHAN M., 2019).

The concept of “cannabic psychosis”, which would imply a specific psychiatric pathology, has been questioned by several researchers. Based on several hypotheses and theories, it was concluded that this alleged specific psychosis does not exist, since no distinct clinical characteristics were found that would make it truly relevant. In addition, researchers emphasize the interaction and importance of preventing cannabis use in individuals with a genetic predisposition to the development of psychosis (GAGE S. et al., 2016).

Although the data are limited in some respects, some associations have been observed: cannabis users are more likely to develop psychotic illnesses (HINDLEY G. et al., 2020); any lifetime use of cannabinoids increases the risk of psychosis by 3.4 times; the age of onset of psychotic illnesses in cannabis users is lower compared to those who have never used the substance (HASAN A. et al., 2019). In addition, the use of cannabis is also related, although there are few studies about it, to the development of bipolar affective disorder, anxiety disorders, depression and increased risk of suicide (SIDELI L. et al., 2019).

## FINAL CONSIDERATIONS

The literature corroborates the impact of psychotic disorders on the quality of life of individuals and the complex correlation between the use of cannabinoids and the development of such disorders. Recently, advances have been achieved, allowing the understanding of the mechanisms of action of cannabinoids, and their adverse effects, in particular, the increased risk of psychosis and schizophrenia. Despite this, the biological mechanisms underlying this association still require further understanding. Future research must focus on deepening the

knowledge of the dose-response relationship between cannabinoids and psychosis, analyzing the interaction between genetic factors, age at initiation of cannabis use and the actual development of psychotic symptoms. Such investigations are crucial for the development of more effective preventive and therapeutic measures for those at risk of

developing such disorders, and also for the therapeutic management of those who are already dealing with these conditions. While cannabis may have potential medicinal uses, recreational use, particularly in younger and genetically predisposed populations, poses significant risks to mental health.

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